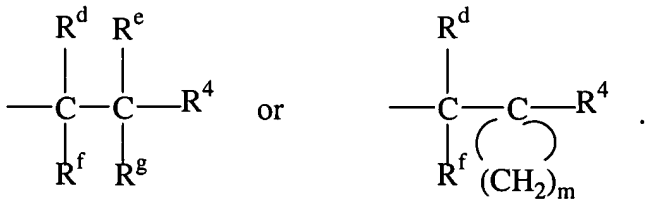
Rejection of Claim 19 for Obviousness-Type Double Patenting

Claims 1 and 19 of the present application have been rejected under the judicially created doctrine of obviousness-type double patenting in view of Claims 1 and 13, respectively, of U.S. Patent No. 6,265,382, which issued from the parent application to the present application, U.S. Serial No. 09/331,876.

In parent application Serial No. 09/331,876, a restriction requirement under 35 U.S.C. 121 was given between the two variables for the moiety R^2, shown below:



In the parent application Applicants prosecuted the compounds of Group I in which R^2 is the first variable. By amendment herein Applicants have limited the compounds of Claim 1 to those of Group II in the original restriction requirement, which encompasses the carbocyclic compounds wherein R^2 is the second moiety shown above.

The third sentence of 35 U.S.C. § 121 states:

> "A patent issuing on an application with respect to which a requirement for restriction under this section has been made, or on an application filed a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application or against the original application or any patent issued on either of them, if the divisional application is filed before the issuance of the patent on the other application."

The present application was filed on October 4, 2000, prior to the July 24, 2001 issue date of U.S. Patent No. 6,265,382.

In view of the restriction requirement in parent application Serial No. 09/331,876 and Applicants amendments herein, Applicants ask that the rejection of Claims 1 and 19 for obviousness-type double patenting be withdrawn.

Rejection of Claims 19 and 25 under 35 U.S.C. 112, First Paragraph

Claims 19 and 25 are rejected under 35 U.S.C. 112, first paragraph. As Claim 25 has been deleted, Applicants will address only the remaining matter of Claim 19.

Applicants have amended Claim 19 to properly indicate the pharmaceutical composition claimed contains a therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier. The present rejection states Claim 19 contains subject matter:

> "which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
>
> As indicated previously, applicant have shown (pp. 52-56) that the compound of examples 1-8 exhibit some propensity to inhibit ras farnesyl transferase *in vitro*. However, this is not sufficient to enable therapeutic method claims, or claims drawn to pharmaceutical compositions."

Applicants respectfully disagree with the basis for this rejection as the present application clearly supports Claim 19 under 35 U.S.C. 112, first paragraph. Applicants respectfully note:

a) the present application sufficiently describes the present invention as to enable any person skilled in the art to make and use the invention;

b) the present rejection is not commensurate with the utility standards of 35 U.S.C. 101 and 112, first paragraph;

c) the utility of inhibiting protein farnesyl transferase has been the subject of considerable scientific research, publication and patent activity and is accepted in the art; and

c) the *in vitro* tests described in the present specification for determination of protein farnesyl transferase inhibition are known and accepted in the art.

The Description in the Present Specification

35 U.S.C. 112, first paragraph, requires an applicant to sufficiently describe the his claimed invention to enable any person skilled in the art to make and use the invention and to disclose the best mode contemplated for carrying out the invention.

The present application teaches compounds which serve as the active ingredient in the pharmaceutical composition of Claim 19, as well as methods for making them and specific examples of compound synthesis within the genus of compounds considered.

From page 14, final paragraph, to page 17, the specification teaches numerous useful pharmaceutical formulations, as well as carriers and excipients which may be used therein. The formulations include parenteral formulations (page 15), solid and liquid forms (pages 15-16), suspensions (page 17), and rectal and vaginal suppositories (page 17). In the final full paragraph of page 17, the specification describes dose ranges useful in the above-mentioned formulations.

Applicants respectfully submit the present specification meets the disclosure requirements of 35 U.S.C. 112, first paragraph.

Utility Standards for 35 U.S.C. 101 and 112, First Paragraph

Applicants also submit the present rejection asks for a utility standard for a pharmacological composition not required under 35 U.S.C. 112, first paragraph, or, more appropriately, under 35 U.S.C. 101.

The present rejection characterizes the compounds of Examples 1-8 as being able to:

"exhibit some propensity to inhibit ras farnesyl transferase *in vitro*. However this is not sufficient to enable the therapeutic claims, or claims drawn to pharmaceutical compositions."

The present rejection does not state what is sufficient to enable pharmaceutical composition claims. As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980).

The standard for pharmacological utility was described by the CCPA in Nelson v. Bowler, 626 F.2d 853, 856, 206 USPQ 881, 883 (1980) as:

"Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility."

The standard set by the CCPA in Nelson v. Bowler was reiterated by the Federal Circuit in Cross v. Iizuka, 224 USPQ 739, at 748, where the court writes:

"We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, in vitro testing, may establish a practical utility for the compound in question. Successful in vitro testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility. Cf. Nelson, 626 F.2d. at 856, 206 USPQ at 883."

Citing these cases, the MPEP at 2107.01, Section III, page 2100-34 (August 2001 Edition), summarizes 'As such, pharmacological or therapeutic inventions that provide any "immediate benefit to the public" satisfy 35 U.S.C. 101.'

Applicants believe the data provided in the present specification clearly meets these standards for the pharmacological activity of inhibiting protein farnesyl transferase.

Acceptance of Protein Farnesyl Transferase Inhibition Activity in the Art

Inhibition of protein farnesyl transferase is an accepted utility in the pharmacological arts, as demonstrated by the references cited in Applicants' response of April 3, 2002.

Applicants wish to note that this utility continues to be accepted in the art, as evidenced by U.S. Patent Application No. 2002/0128280 A1 (Daley), published September 12, 2002, and U.S. Patent Application 2003/0050323 A1 (Rybak), published March 13, 2003, copies of which are enclosed.

Acceptance of In Vitro Assays of the Present Specification

Applicants also wish to note the *in vitro* tests for farnesyl transferase inhibition discussed in the present application are known and accepted in the art. As evidence, Applicants note the inhibition of ras protein farnesylation demonstrated in H-ras-transformed NIH 3T3 cells, as discussed on page 55. This assay has long been recognized as a standard in the art, as demonstrated in the following disclosures, copies of which are enclosed:

1) DeClue et al. describe the use of a ras-transformed NIH3T3 cell line in their article *Inhibition of Cell Growth by Lovastatin Is Independent of ras Function*, Cancer Research 51, 712-717, January 15, 1991.

2) The article *Ras Farnesylation as a Target for Novel Antitumor Agents: Potent and Selective Farnesyl Diphosphonate Analog Inhibitors of Farnesyltransferase*, Manne et al.,

Drug Development Research, 34:121-137 (1995), discusses the ability of a pivaloyloxymethyl ester of a farnesyl pyrophosphate analog to block ras mediated transformation of NIH 3T3 cells.

3) The article *Inhibition of the prenylation of K-Ras, but not H- or N-Ras, is highly resistant to CAAX peptidomimetics and requires both a farnesyltransferase and a geranylgeranyltransferase I inhibitor in human tumor cell lines*, Lerner et al., Oncogene (1997), 15, 1283-1288, (Received 28 February 1997), discusses the ability of the farnesyltransferase inhibitor FTI-277 to inhibit N-Ras prenylation in both natural and transfected NIH3T3 cells (see page 1286, bottom of second column).

4) Earlier useof Ha-ras-transformed NIH3T3 fibroblasts in an assay for the inhibition of Ras processing can be seen in the article *Selective Inhibition of Farnesyl-Protein Transferase Blocks Ras Processing in Vivo*, Gibbs et al., The Journal of Biological Chemistry, Vol. 268, No. 11, Issue of April 15, 7617-7620, 1993.

5) and 6) Example 16 of WO 96/34010 (DeSolms) and Example 32 of WO 96/10011 (Stocker et al.) describe the use of ras-transformed NIH3T3 cells for determinations of percent inhibition of farnesyl transfer to protein by various agents.

To demonstrate the continued use of this technique today, Applicants enclose a copy of Example 12 of U.S. Patent No. 6,525,074, issued February 25, 2003.

The present rejection also calls into question the acceptance of farnesyltransferase inhibition in the art. For instance, the rejection questions the utility of farnesyl transferase inhibitor R115777, stating:

> "Sharma also quotes another scientist (Skrzat, S.) as asserting that R115777 inhibited growth of human tumor xenographs of colon cancer in unspecified animals. No further information is given. Perhaps R115777 caused actual reduction of tumor volumes. Or perhaps R115777 was only cytostatic, and the animals died anyway. Or perhaps results were obtained which appeared on the

surface to indicate efficacy, but the results were not statistically significant. Finally, applicants have pointed to Tolcher (Oncologist 6 Suppl 3 40-4, 2001) who conveys that a few FT inhibitors are the subject of clinical trials. However, there is no conclusive evidence of efficacy."

Applicants respectfully submit this argument is not based on the reference's disclosure. Rather, it is only supposition of what might not have been included. As for additional evidence of the utility of protein farnesyl transferase inhibitors, in general, and R115777, in particular, Applicants enclose a copy of Current Opinion in Investigational Drugs 2002 Vol. 3 No. 2, which describes the current Phase III human trials for R115777. The second paragraph of the article discusses predictions of NDA filings for R115777 in 2002 and 2003 for pancreatic cancer and other cancers, and projected U.S. introductions for these indications in 2004 and 2005, respectively.

In view of the foregoing, Applicants submit that the present claims fully meet the requirements of 35 U.S.C. 112, first paragraph, and respectfully ask that this rejection be withdrawn.

Rejection of Claims 1-19, 24 and 25 under 35 U.S.C. 112, Second Paragraph

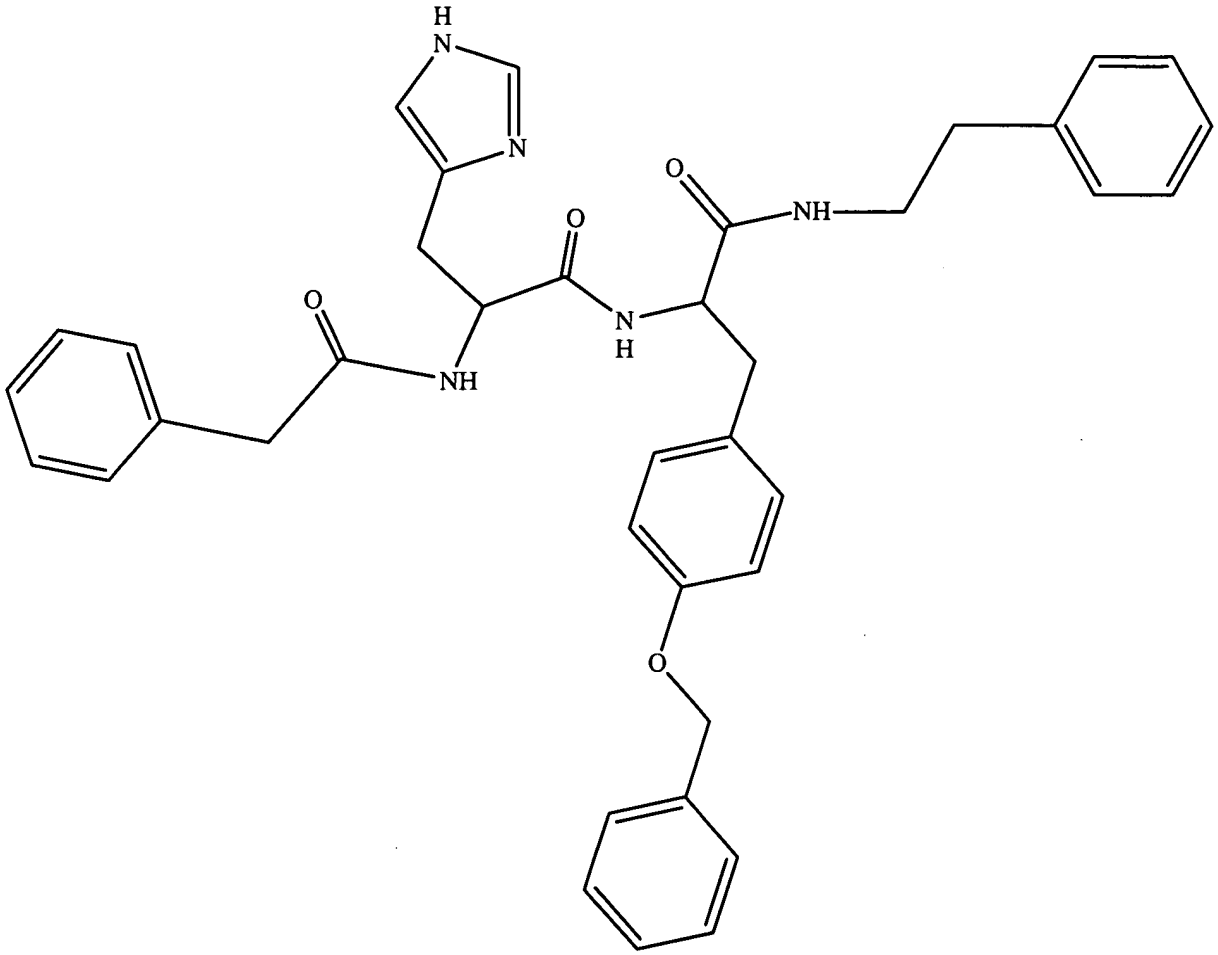
Claims 1-19, 24 and 25 are rejected under 35 U.S.C. 112, Second Paragraph. In view of the amendments herein to Claims 1-19 and the deletion of Claims 24 and 25, Applicants ask that this rejection be withdrawn.

Rejection of Claims 1, 2, 5, 7 and 19 under 35 U.S.C. 102(e)

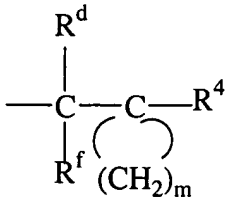
Claims 1, 2, 5, 7 and 19 have been rejected under 35 U.S.C. 102(e) as anticipated by Compound No. 26 in Column 19 of U.S. Patent No. 5,830,868 (Bolton et al.). Applicants respectfully disagree with this rejection.

The rejection states that the Bolton et al. compound, listed as "$PhCH_2CO$-D-His-Tyr(Obn)$CONHCH_2CH_2Ph$" anticipates the compounds of the present invention. Applicants

submit the initial "CO" of the name indicates a carbonyl group, rather than a compound in which the variable "Y" is O, as mentioned in the present rejection. The compound listed by Bolton et al. would appear as:



Applicants also wish to note that the other end of the cited compound No. 26, listed as "-$CONHCH_2CH_2Ph$" would not anticipate the compounds of amended Claim 1 wherein the moiety R^2 is limited carbocycle-containing groups of the formula:



In view of the differences between the compound disclosed by Bolton et al. and those of the presently claimed invention, withdrawal of this rejection under 35 U.S.C. 102(e) is respectfully requested.

In view of the foregoing, Applicants believe the present application is now in condition for allowance and respectfully solicit a decision to that effect.

Respectfully submitted,

Dated: March 27, 2003

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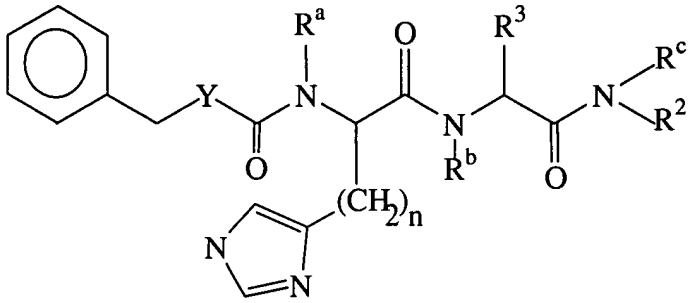
Enclosures:

1) Cancer Research 51, 712-717, January 15, 1991.
2) Drug Development Research, 34:121-137 (1995)
3) Oncogene (1997), 15, 1283-1288
4) J. Biol. Chem., Vol. 268, No. 11, Issue of April 15, 7617-7620, 1993.
5) Example 16 of WO 96/34010 (DeSolms)
6) Example 32 of WO 96/10011 (Stocker et al.)
7) Example 12 of U.S. Patent No. 6,525,074
8) Current Opinion in Investigational Drugs 2002 Vol. 3 No. 2, pp. 313-319
9) U.S. 2002/0128280 A1 (Daley)
10) U.S. 2003/0050323 A1 (Rybak)

Marked-Up Copy of Amendments

IN THE CLAIMS

1. A [C]ompound[s] having the Formula I



I

wherein:

R^a, R^b, R^c are each independently C_1-C_6 alkyl or hydrogen;

R^d, R^e, R^f, and R^g are each independently C_1-C_6 alkyl, hydrogen, or phenyl;

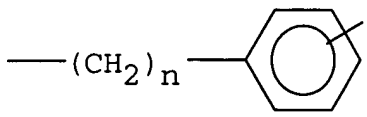
Y is -O-, -N-, or -N-;

| | |

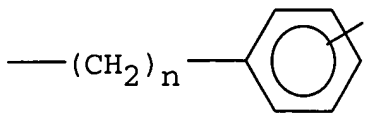
H C_1-C_6 alkyl;

R^3 is

—$(CH_2)_n$—phenyl ,



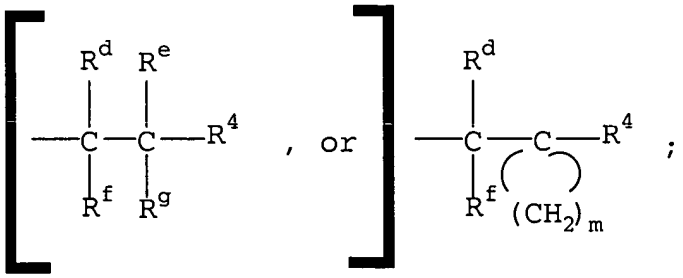
—$(CH_2)_n$—C_1-C_6 alkyl ,



, or

—$(CH_2)_n$—substituted phenyl ;

R^2 is



R^4 is aryl, substituted aryl, or C_1-C_6 alkyl; and

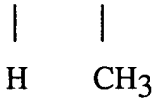
each n is independently 0 to 5, m is 2 to 4 [and the] or a pharmaceutically acceptable salt[s, and] or prodrug[s] form thereof.

2. [A compound according to] The compound of Claim 1 wherein

Y is -O-.

3. [A compound according to] The compound of Claim 1 wherein

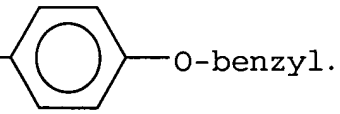
Y is -N- or -N-.



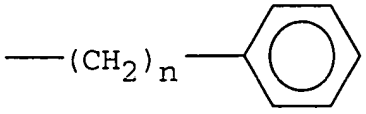
4. [A compound according to] The compound of Claim 1 wherein R^a is hydrogen, R^b is methyl,

and R^c is hydrogen.

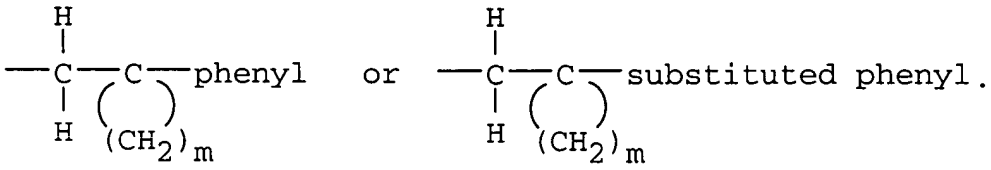
5. [A compound according to] The compound of Claim 1 wherein

R^3 is  .

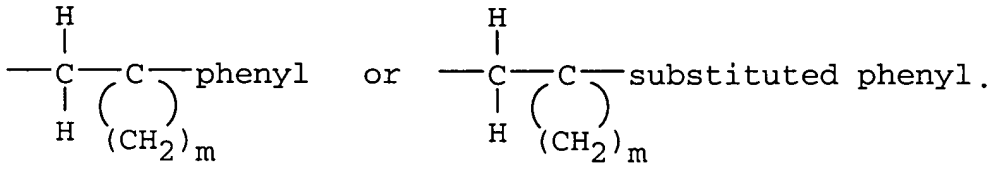
6. [A compound according to] The compound of Claim 1 wherein R^3

 .

7. [A compound according to] The compound of Claim 1 wherein

R^2 is  or .

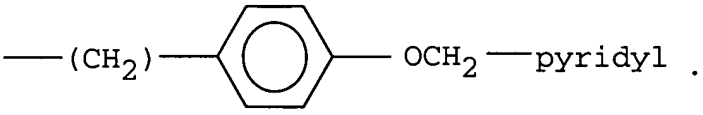
10. [A compound according to] The compound of Claim 9 wherein m of

 or .

m is 3 or 4.

8. [A compound according to] The compound of Claim 1 wherein R^3 is $-(CH_2)_n-C_1-C_6$ alkyl.

9. [A compound according to] The compound of Claim 1 wherein

R^3 is  .

14. The compounds:

[[S-(R*,R*)]-[1-({2-(4-Benzyloxy-phenyl)-1-[2-(2-fluoro-phenyl)-ethyl-carbamoyl]-ethyl}-methyl-carbamoyl)-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester;

[S-(R*,R*)]-[1-{[2-(4-Benzyloxy-phenyl)-1-(2-pyridin-2-yl-ethyl-carbamoyl)-ethyl]-methyl-carbamoyl}-2-(3 H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester;

[S-(R*,R*)]-[1-{[2-(4-Benzyloxy-phenyl)-1-(2,2-diphenyl-ethylcarbamoyl)-ethyl]-methyl-carbamoyl}-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester;

[S-(R*,R*)]-[1-{[2-(4-Benzyloxy-phenyl)-1-(2-phenyl-propylcarbamoyl)-ethyl] -methyl-carbamoyl}-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester;

[S-(R*,R*)]-(2-(3H-Imidazol-4-yl)-1-{methyl-[3-methyl-1-(2-methyl-2-phenyl-propylcarbamoyl)-butyl]-carbamoyl}-ethyl)-carbamic acid benzyl ester;

[S-(R*,R*)]-[1-{[2-(4-Benzyloxy-phenyl)-1-(1-methyl-2-phenyl-ethylcarbamoyl)-ethyl]-methyl-carbamoyl}-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester;]

[S-(R*,R*)]-[1-({2-(4-Benzyloxy-phenyl)-1-[(1-phenyl-cyclopropyl-methyl)-carbamoyl]-ethyl}-methyl-carbamoyl)-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester;

[[S-(R*,R*)]-[1-{[2-(4-Chloro-phenyl)-1-(2-methyl-2-phenyl-propylcarbamoyl)-ethyl]-methyl-carbamoyl}-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester;

[S-(R*,R*)]-2-(3-Benzyl-ureido)-3-(3H-imidazol-4-yl)-N-methyl-N-{1-(2-methyl-propyl-carbamoyl)-2-[4-(pyridin-4-ylmethoxy)-phenyl]-ethyl}-propionamide;

[S-(R*,R*)]-[1-{[2-(4-Benzyloxy-phenyl)-1-(1-methyl-2-phenyl-ethylcarbamoyl)-ethyl]-methyl-carbamoyl}-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester;

[S-(R*,R*)]-(2-(3H-Imidazol-4-yl)-1-{methyl-[1-(2-methyl-2-phenyl-propylcarbamoyl)-2-p-tolyl-ethyl]-carbamoyl}-ethyl)-carbamic acid benzyl ester;

[S-(R*,R*)]-(2-(3H-Imidazol-4-yl)-1-{[2-(4-methoxy-phenyl)-1-(2-methyl-2-phenyl-propylcarbamoyl)-ethyl]-methyl-carbamoyl}-ethyl)-carbamic acid benzyl ester;

[S-(R*,R*)]-2-(3-Benzyl-ureido)-3-(3H-imidazol-4-yl)-N-methyl-N-[1-(2-methyl-2-phenyl-propylcarbamoyl)-2-phenyl-ethyl]-propionamide; and]

[S-(R*,R*)]-[1-[(2-(4-Benzyloxy-phenyl)-1-{[1-(2-fluoro-phenyl)-cyclopropylmethyl]-carbamoyl}ethyl)-methyl-carbamoyl]-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester[.] ; and

[S-(R*,R*)]-[1-{[2-(4-Benzyloxy-phenyl)-1-[(1-phenyl-cyclobutylmethyl)-carbamoyl]-ethyl}-methyl-carbamoyl)-2-(3H-imidazol-4-yl)-ethyl]-carbamic acid benzyl ester;

19. A pharmaceutical composition [that] compris[es]ing a therapeutically effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.